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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BONDINELL, William, E. [US/US]; 1512 Franklin Lane, Wayne, PA 19087 (US). KU, Thomas, W. [US/US]; 1413 Southwind Way, Dresher, PA 19025 (US). WANG, Ning [CN/US]; 708 Lexington Drive, Phoenixville, PA 19460 (US).

(74) Agents: STEIN–FERNANDEZ, Nora et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406–0939 (US).

(54) Title: COMPOUNDS AND METHODS

(57) Abstract

This invention relates to substituted benzanilides which are modulators, agonists or antagonists, of the CCR5 receptor. In addition, this invention relates to the treatment and prevention of disease states mediated by CCR5, including, but not limited to, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease, all in mammals, by the use of substituted benzanilides which are CCR5 receptor antagonists. Furthermore, since CD8+ T cells have been implicated in COPD, CCR5 may play a role in their recruitment and therefore antagonists to CCR5 could provide potential therapeutic in the treatment of COPD. Also, since CCR5 is a co–receptor for the entry of HIV into cells, selective receptor modulators may be useful in the treatment of HIV infection.

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COMPOUNDS AND METHODS

FIELD OF THE INVENTION

This invention relates to substituted benzanilides which are modulators, agonists or antagonists, of the CC chemokine receptor CC-CKR5 now designated as CCR5 (*Nature Medicine* **1996**, *2*, 1174-8). In addition, this invention relates to the treatment and prevention of disease states mediated by CCR5.

BACKGROUND OF THE INVENTION

T cells are not only key regulators of the immune response to infectious agents but are believed critical for the initiation and maintenance of the inflammatory reaction in a variety of chronic diseases. Increased numbers or enhanced activation state of T cells, especially CD4+ T cells, have been demonstrated in the synovium of individuals with rheumatoid arthritis (M.J. Elliott and R. N. Maini, Int. Arch. Allergy Immunol. 104: 112-1125, 1994), in the bronchial mucosa of asthmatics (C.J. Corrigan and A.B. Kay, Immunol. Today 13:501-506, 1992), in the lesions of multiple sclerosis (R. Martin and H. F. McFarland, Crit. Rev. Clin. Lab. Sci. 32: 121-182, 1995), in psoriatic lesions (J.L. Jones, J. Berth-Jone, A. Fletcher and P.E. Hutchinson, J. Pathol. 174: 77-82, 1994) and in the fatty streaks of atherosclerosis (R. Ross, Annu. Rev. Physiol. 57: 791-804, 1995).

T cells, as well as other inflammatory cells, will migrate into tissues in response to the production of a variety chemotactic factors. Among these factors are a superfamily of 8-12 kDa proteins known as the chemokines. These proteins share structural features such as the presence of 3-4 conserved cysteine residues. RANTES, which stands for Regulated upon Activation Normal T cell Expressed and Secreted, is a 8 kDa protein member of CC branch of the chemokine family. These proteins recruit and activate immune and inflammatory cells through an interaction with G-protein coupled receptors. The CC branch is defined by the absence of an intervening amino acid residue between the first two cysteine residues and members of this family predominately elicit the migration of mononuclear cells, eosinophils and basophils (M. Baggiolini, B. Dewald, and B. Moser, Adv. Immunol. 55: 97-179, 1994; and J.J. Oppenheim, C.O.C. Zachariae, N. Mukaida, and K. Matsushima, Annu. Rev. Immunol. 9: 617-648, 1991).

RANTES potently produces chemotaxis of T cells, basophils, eosinophils, monocytes and mast cells. RANTES was originally identified as gene product induced late after antigen activation of T-cells (T.J. Schall, J. Jongstra, B.J. Dyer, J.

Jorgensen, et al., J. Immunol. 141:1018-1025, 1988), however, RANTES has been shown to be synthesized and secreted by a diverse group of cells that include epithelial and endothelial cells (C. Stellato, L.A. Beck, G.A. Gorgone, D. Proud, et al., J. Immunol. 155: 410-418, 1995; and A. Marfaing-Koka, O. Devergne, G. Gorgone, A. Portier, et al., J. Immunol. 154: 1870-1878, 1994), synovial fibroblasts (P. Rathanaswami, M. Hachicha, M. Sadick, T.J. Schall, et al., J. Biol. Chem. 268: 5834-5839, 1993) and dermal fibroblasts (M. Sticherling, M. Kupper, F. Koltrowitz, E. Bornscheuer, et al., J. Invest. Dermatol. 105: 585-591, (1995), mesangial cells (G. Wolf, S. Aberle, F. Thaiss, et al., Kidney Int. 44: 795-804, 1994) and platelets (Y. Koameyoshi, A. Dorschner, A.I. Mallet, E. Christophers, et al., J. Exp. Med. 176: 587-592, 1992). In these cells RANTES mRNA is rapidly upregulated in response to IL-1 or TNFa. Although RANTES mRNA is not usually detected in normal tissues (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995), increased mRNA or protein has been found in diseases characterized by a mononuclear infiltrate. For example, RANTES mRNA was visualized using *in situ* hybridization in renal allografts undergoing rejection (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995; and K.C. Nadeau, H. Azuma and N.I. Tilney, Proc. Natl. Acad. USA 92: 8729-8733, 1995) in the skin of atopic dermatitis patients after exposure to antigen (S. Ying, L. Taborda-Barata, Q. Meng, M. Humbert, et al., J. Exp. Med. 181: 2153-2159, 1995), and in endothelial cells of coronary arteries undergoing accelerated atherosclerosis after cardiac transplant (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995). Further, increased immunoreactive protein for RANTES has been detected in bronchoalveolar lavage fluid (R. Alam, J. York, M. Boyers, et al., Am. J. Resp. Crit. Care Med. 149: A951, 1994) and sputum from asthmatic individuals (C.M. Gelder, P.S. Thomas, D.H. Yates, I.M. Adcock, et al., Thorax 50: 1033-1037, 1995).

Several receptors have been identified that bind RANTES. In particular, CCR5, when expressed in either HEK 293 cells or CHO cells, binds RANTES. This receptor is expressed in T-cells and in monocytes and macrophages, immune/inflammatory cells which are important in the maintenance of a chronic inflammatory reaction. Pharmacological characterization of CCR5 indicates similarities to the RANTES binding site observed on isolated T cells. Therefore, antagonism of RANTES' action on CCR5, as well as antagonism of other natural modulators of CCR5, should inhibit the recruitment of T cells and macrophages into inflammatory lesions and provide a novel therapeutic approach for the treatment of atopic and autoimmune disorders.

Since T cells express CCR5, selective receptor modulators of CCR5, particularly antagonists, are likely to provide beneficial effects in diseases including, but not limited to, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease, all in mammals, preferably humans. Furthermore, since CD8+ T cells have been implicated in chronic obstructive pulmonary disorders (COPD), CCR5 may play a role in their recruitment and therefore antagonists to CCR5 could provide potential therapeutic in the treatment of COPD. Also, since CCR5 is a co-receptor for the entry of HIV into cells, selective receptor modulators may be useful in the treatment of HIV infection.

A subset of compounds included in formula (I) have been reported to have 5-HT receptor activity (international application publication number WO 95/15954, published 15 June 1995, international application publication number WO 95/17398, published 29 June 1995, international application publication number WO 95/26328, published 5 October 1995, international application publication number WO 96/06079, published 29 February 1996, GB 2276161 published 21 September 1994, and GB 2276165 published 21 September 1994; international application publication number WO 95/30675 published 16 November 1995;international application publication number WO 95/17401 published 29 June 1995;international application publication number WO 96/31508 published 10 October 1996; international application publication number WO 97/10824 published 27 March 1997; international application publication number WO 96/11934 published 25 April 1996; international application publication number WO 96/19477 published 27 June 1996; international application publication number WO 97/17350 published 15 May 1997; international application publication number WO 97/34900 published 25 September 1997; international application publication number WO 97/34901 published 25 September 1997; international application publication number WO 97/35862 published 2 October 1997; international application publication number WO 97/19070 published 29 May 1997; international application publication number WO 95/32967 published 7 December 1995; international application publication number WO 97/07120 published 27 February 1997; U.S. Patent 3,931,195, issued Jan. 6, 1976; and U.S. Patent 4,000,143, issued Dec. 28, 1976). In addition, WO 99/01127, published January 14, 1999, discloses substituted benzanilides useful for modulating CCR5-mediated diseases.

Surprisingly, it has now been discovered that this class of non-peptide compounds, in particular substituted benzanilides of formula (I), function as CCR5

receptor modulators, and therefore, have utility in the treatment and prevention of disease states mediated by CCR5 receptor mechanisms.

SUMMARY OF THE INVENTION

The present invention is to compounds of formula (I) and their use as CCR5 modulators for the treatment of certain disease states, including, but not limited to, COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection, all in mammals, preferably humans. Compounds of formula (I) have been described in copending patent application Attorney Docket No. P50680, provisional application serial number 60/051,632, filed July 3, 1997, published as international application WO 99/01127 on January 14, 1999. The preferred compounds for use as CCR5 modulators herein are those compounds of formula (I) as noted.

DETAILED DESCRIPTION OF THE INVENTION

It has now been discovered that substituted benzanilides of formula (I) are particularly potent CCR5 receptor modulators. Selective inhibition of CCR5 receptor mechanisms by treatment with the receptor modulators of formula (I), or a pharmaceutically acceptable salt thereof, represents an effective therapeutic and preventative approach to the treatment of a variety of disease states, including, but not limited to, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease, all in mammals, preferably humans. Furthermore, since CD8+ T cells have been implicated in COPD, CCR5 may play a role in their recruitment and therefore antagonists to CCR5 could provide potential therapeutic in the treatment of COPD. Also, since CCR5 is a co-receptor for entry into cells, selective receptor modulators may be useful in the treatment of HIV infection.

Compounds for use herein as CCR5 modulators include the 5-HT ligands as described in international application publication number WO 95/15954, published 15 June 1995, (USSN 08/652,581, filed June 7, 1996); international application publication number WO 95/17398, published 29 June 1995, (USSN 08/663,291, filed June 21, 1996); international application publication number WO 95/26328, published 5 October 1995, (USSN 08/718,481, filed Sept. 26, 1996); international application publication number WO 96/06079, published 29 February 1996, (USSN

08/793,428, filed Feb. 21, 1997); GB 2276161 published 21 September 1994, and GB 2276165 published 21 September 1994; international application publication number WO 95/30675, published 16 November 1995, (USSN 08/737,147); international application publication number WO 95/17401, published 29 June 1995 (USSN 08/663,290, filed June 21, 1996); international application publication number WO 96/31508, published 10 October 1996 (USSN 08/930,848, filed Oct. 7, 1997); international application publication number WO 97/10824, published 27 March 1997 (USSN 09/043,346); international application publication number WO 96/11934, published 25 April 1996, (USSN 08/817,619); international application publication number WO 96/19477, published 27 June 1996 (USSN 08/849,932); international application publication number WO 97/17350, published 15 May 1997 (USSN 09/068,382, filed May 8, 1998); international application publication number WO 97/34900, published 25 September 1997; international application publication number WO 97/34901, published 25 September 1997; international application publication number WO 97/35862, published 2 October 1997; international application publication number WO 97/19070, published 29 May 1997 (USSN 09/077,263); international application publication number WO 95/32967, published 7 December 1995 (USSN 08/737,660); international application publication number WO 97/07120, published 27 February 1997 (USSN 09/011,338, filed Feb. 11, 1998); U.S. Patent 3,931,195, issued Jan. 6, 1976; and U.S. Patent 4,000,143, issued Dec. 28, 1976.

Preferred compounds for use as CCR5 modulators are those compounds of Formula (I) as noted herein.

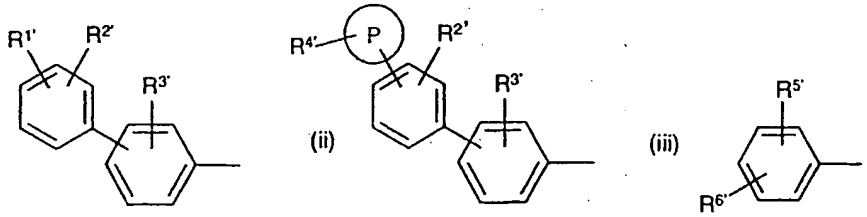
Each of these references is incorporated herein in their entirety.

A preferred group of compounds for use herein are those compounds of the formula (I) or a pharmaceutically acceptable salt thereof:

Ar—A—E

Formula I

in which Ar represents a group selected from (i), (ii) or (iii);



wherein:

the basic nitrogen in moiety E may be optionally be quaternized with C_{1-6}alkyl or is optionally present as the N-oxide;

$R^{1'}$ and $R^{2'}$ are independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{3-6}cycloalkenyl, aryl, $(CH_2)_aNR^{7'}R^{8'}$, $(CH_2)_aNR^{7'}COR^{9'}$, $(CH_2)_aNR^{7'}CO_2R^{10'}$, $(CH_2)_aNR^{7'}SO_2R^{11'}$, $(CH_2)_aCONR^{12'}R^{13'}$, hydroxy$C_{1-6}$alkyl, C_{1-4}alkoxyalkyl (optionally substituted by a C_{1-4}alkoxy or hydroxy group), $(CH_2)_aCO_2C_{1-6}$alkyl, $(CH_2)_bOC(O)R^{14'}$, $CR^{15'}=NOR^{16'}$, $CNR^{15'}=NOR^{16'}$, $COR^{17'}$, $CONR^{12'}R^{13'}$, $CONR^{12'}(CH_2)_cOC_{1-4}$alkyl, $CONR^{12'}(CH_2)_aCO_2R^{18'}$, $CONHNR^{19'}R^{20'}$, $CONR^{12'}SO_2R^{21'}$, $CO_2R^{22'}$, cyano, trifluoromethyl, $NR^{7'}R^{8'}$, $NR^{7'}COR^{9'}$, $NR^{23'}CO(CH_2)_aNR^{23'}R^{24'}$, $NR^{23'}CONR^{23'}R^{24'}$, $NR^{7'}CO_2R^{10'}$, $NR^{7'}SO_2R^{11'}$, $N=CNR^{23'}NR^{23'}R^{24'}$, nitro, hydroxy, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, $OC(O)NR^{25'}R^{26'}$, $SR^{27'}$, $SOR^{28'}$, $SO_2R^{28'}$, $SO_2NR^{25'}R^{26'}$ or halogen;

$R^{3'}$ and $R^{4'}$ are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}cycloalkenyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{1-6}alkyl, $CONR^{29'}R^{30'}$, $CO_2R^{31'}$, cyano, aryl, trifluoromethyl, $NR^{29'}R^{30'}$, nitro, hydroxy, C_{1-6}alkoxy, acyloxy or halogen;

$R^{5'}$ is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy or halogen;

$R^{6'}$ is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl (optionally substituted by a hydroxy or an oxo group), hydroxyC_{1-6}alkyl, hydroxyC_{3-6}alkenyl, hydroxyC_{3-6}alkynyl, $(CH_2)_dOR^{32'}$, $(CH_2)_dCOR^{33'}$, $(CH_2)_dCR^{34'}=NOR^{35'}$, $CONR^{36'}R^{37'}$, $CO_2R^{38'}$, hydroxy, $O(CH_2)_eR^{39'}$, $NR^{36'}R^{37'}$, $SR^{40'}$, $SO_2NR^{41'}R^{42'}$ or halogen; or, $R^{5'}$ and $R^{6'}$ form a fused benzo ring optionally substituted with C_{1-6} alkyl, C_{1-6}alkoxy or halogen;

$R^{7'}$ and $R^{8'}$ are independently hydrogen or C_{1-6}alkyl, or together with the nitrogen to which they are attached, $R^{7'}$ and $R^{8'}$ form a 5- to 6-membered heterocyclic ring, which ring may optionally be substituted by an oxo group and, which, when the ring is 6-membered, may optionally contain in the ring one oxygen or sulfur atom;

$R^{9'}$ is hydrogen, C_{1-6}alkyl or C_{1-4}alkoxyalkyl;

$R^{10'}$ is C_{1-6}alkyl;

$R^{11'}$ is C_{1-6}alkyl or phenyl;

$R^{12'}$ and $R^{13'}$ are independently hydrogen or C_{1-6}alkyl, or together with the nitrogen to which they are attached, $R^{12'}$ and $R^{13'}$ form a 5- to 6-membered heterocyclic ring, which, when the ring is 6-membered, may optionally contain in the ring one oxygen or sulfur atom;

$R^{14'}$ is C_{1-4}alkyl, optionally substituted by C_{1-6}alkoxy;

$R^{15'}$ and $R^{16'}$ are independently hydrogen or C_{1-6}alkyl;

$R^{17'}$ is hydrogen or C_{1-6}alkyl;

$R^{18'}$ is hydrogen or C_{1-6}alkyl;

$R^{19'}$ and $R^{20'}$ are independently hydrogen or C_{1-6}alkyl;

$R^{21'}$ is hydrogen or C_{1-6}alkyl;

$R^{22'}$ is hydrogen or C_{1-6}alkyl optionally substituted with one or two substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, or $NR^{7'}R^{8'}$;

$R^{23'}$ and $R^{24'}$ are independently hydrogen or C_{1-6}alkyl;

$R^{25'}$ and $R^{26'}$ are independently hydrogen or C_{1-6}alkyl, or together with the nitrogen to which they are attached, $R^{25'}$ and $R^{26'}$ form a 5- to 6-membered heterocyclic ring, which, when the ring is 6-membered, may optionally contain in the ring one oxygen or sulfur atom;

$R^{27'}$ is hydrogen or C_{1-6}alkyl;

$R^{28'}$ is C_{1-6}alkyl;

$R^{29'}$, $R^{30'}$ and $R^{31'}$ are independently hydrogen or C_{1-6}alkyl;

$R^{32'}$ is C_{1-6}alkyl, hydroxyC_{1-6}alkyl, or C_{1-4}alkanoyl;

$R^{33'}$ is hydrogen or C_{1-6}alkyl;

$R^{34'}$ is hydrogen or C_{1-6}alkyl;

$R^{35'}$ is hydrogen or C_{1-6}alkyl;

$R^{36'}$ and $R^{37'}$ are independently hydrogen or C_{1-6}alkyl or together with the nitrogen to which they are attached, $R^{36'}$ and $R^{37'}$ form a 5- to 6-membered heterocyclic ring, which ring may be optionally substituted by an oxo group and, which, when the ring is 6-membered, may optionally contain one oxygen or sulfur atom or an NH group or a group $NR^{43'}$, wherein $R^{43'}$ is C_{1-6}alkyl, $COR^{44'}$ or $CO_2R^{45'}$, wherein $R^{44'}$ and $R^{45'}$ are independently hydrogen or C_{1-6}alkyl;

$R^{38'}$ is hydrogen or C_{1-6}alkyl;

$R^{39'}$ is C_{1-6}alkoxy, CO_2H, CO_2C_{1-6}alkyl or $CONR^{36'}R^{37'}$;

$R^{40'}$ is C_{1-6}alkyl;

$R^{41'}$ and $R^{42'}$ are independently hydrogen or C_{1-6}alkyl;

P is a 5 to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur;

a' is 1, 2, 3 or 4;

b' is 0, 1, 2 or 3;

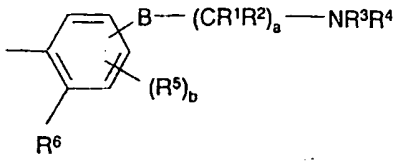
c' is 1, 2 or 3;

d' is 0, 1, 2, 3, 4, 5, or 6; and

e' is 1, 2, 3, 4, 5 or 6;

and further wherein, when Ar is (i), (ii) or (iii), and A is $CONR^{46'}$, NHCO, $-NHCH_2$, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

E represents (a):



(a);

in which

B is oxygen, $S(O)_c$, $CR^7=CR^8$, or CR^7R^8, or B is NR^9;

R^1 and R^2 are independently hydrogen or C_{1-6}alkyl; alternatively $B(CR^1R^2)_a$ is $OCR^1R^2CR^1(OH)CR^1R^2$ or $OCR^1R^2CR^1(OCOCH_3)CR^1R^2$;

R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, hydroxy, $OCOR^{12}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{13}$, and $NHCO_2R^{14}$;

R^5 is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{15}R^{16}$, CO_2R^{17}, trifluoromethyl, $NHCO_2R^{18}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_dR^{19}$, $SO_2NR^{20}R^{21}$ or halogen;

R^6 is hydrogen, C_{1-6}alkyl, aryl, trifluoromethyl, hydroxy, C_{1-6}alkoxy or halogen, or R^6 taken together with $R^{46'}$ forms a group D where D is $(CR^{22}R^{23})_e$ or D is $(CR^{22}R^{23})_f$-G where G is oxygen, sulfur or $CR^{22}=CR^{23}$, $CR^{22}=N$, $=CR^{22}O$, $=CR^{22}S$, or $=CR^{22}-NR^{23}$;

R^7, R^8, R^{10}, R^{11}, R^{12}, R^{15}, R^{16}, R^{17}, R^{20}, R^{21}, R^{22}, and R^{23} are independently hydrogen or C_{1-6}alkyl;

R^9 is hydrogen, C_{1-6}alkyl, or phenylC_{1-6}alkyl;

R^{13}, R^{14}, R^{18}, and R^{19} are independently C_{1-6}alkyl;

a is 1, 2, 3, or 4;

b is 1 or 2;

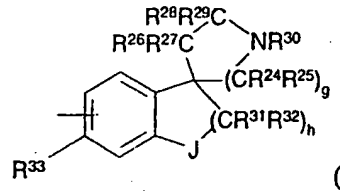
c and d are independently 0, 1 or 2;

e is 2, 3 or 4;

f is 0, 1, 2 or 3;

and further wherein, when Ar is (i), (ii) or (iii), and A is $CONR^{46'}$, NHCO, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

E represents (b):



(b);

R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31}, and R^{32} are independently hydrogen or C_{1-6}alkyl;

R^{30} is hydrogen, C_{1-6}alkyl, or C_{3-6}cycloalkyl;

R^{33} is hydrogen, C_{1-6}alkyl, trifluoromethyl, hydroxy or halogen, or R^{33} and $R^{46'}$ together form a group -K- where K is $(CR^{34}R^{35})_i$ or K is $(CR^{34}R^{35})_j$ -M and M is oxygen, sulfur, $CR^{34}=CR^{35}$, $CR^{34}=N$, or N=N;

J is oxygen, $CR^{36}R^{37}$, or NR^{38}, or J is a group $S(O)_k$;

R^{34}, R^{35}, R^{36}, R^{37}, and R^{38} are independently hydrogen or C_{1-6}alkyl;

g is 1, 2 or 3;

h is 1, 2 or 3;

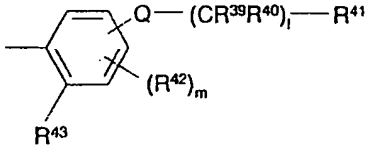
i is 2, 3, or 4;

j is 0, 1, 2, or 3;

k is 0, 1 or 2;

and further wherein, when Ar is (i), (ii) or (iii), and A is $CONR^{46'}$, NHCO, -$NHCH_2$, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

E represents (c):



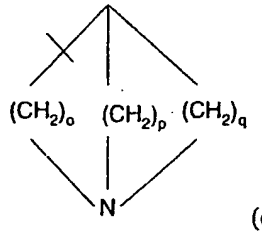
(c);

in which:

Q is oxygen, $S(O)_n$, $CR^{44}=CR^{45}$, $CR^{44}R^{45}$, or Q is NR^{46};

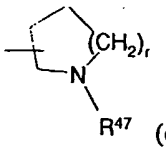
R^{39} and R^{40} are independently hydrogen or C_{1-6}alkyl;

R^{41} is a group of formula (d):



(d)

or R^{41} is a group of formula (e):



(e)

R^{42} is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{48}R^{49}$, CO_2R^{50}, trifluoromethyl, $NHCO_2R^{51}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_sR^{52}$, $SO_2NR^{53}R^{54}$, or halogen;

R^{43} is hydrogen or R^{43} together with $R^{46'}$ forms a group R where R is $CR^{55}=CR^{56}$, $CR^{55}=CR^{56}CR^{55}R^{56}$, or $(CR^{55}R^{56})_t$;

R^{44}, R^{45}, R^{46}, R^{48}, R^{49}, R^{50}, R^{53}, R^{54}, R^{55}, and R^{56} are independently hydrogen or C_{1-6}alkyl;

R^{47} is hydrogen, C_{1-6}alkyl, or C_{3-7} cycloalkyl;

R^{51} and R^{52} are independently C_{1-6}alkyl;

l is 0, 1, 2, or 3;

m is 1 or 2;

n is 0, 1, or 2

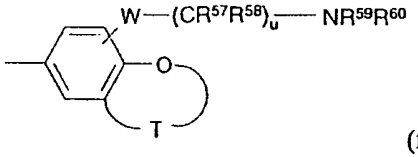
o, p, and q are independently integers having the value 1, 2, or 3;

r is 0,1, 2, or 3;

s is 0, 1, or 2;

t is 2 or 3;

and further wherein, when Ar is (i), (ii) or (iii), and A is CONH, NHCO, or CH_2NH, E represents (f):



(f);

R^{57} and R^{58} are independently hydrogen or C_{1-6}alkyl;

R^{59} and R^{60} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, $CONR^{61}R^{62}$, $NR^{61}R^{62}$, hydroxy, $OCOR^{63}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{64}$, and $NHCO_2R^{65}$;

T is $-(CR^{66}R^{67})_v-$ or $-O(CR^{66}R^{67})_w-$;

W is oxygen, $S(O)_x$, NR^{68}, or W is $CR^{69}=CR^{70}$ or $CR^{69}R^{70}$;

R^{61}, R^{62}, R^{63}, R^{66}, R^{67} R^{68}, R^{69}, and R^{70} are independently hydrogen or C_{1-6}alkyl;

R^{64} and R^{65} are independently C_{1-6}alkyl;

u is 1 to 4;

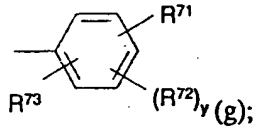
v is 2 or 3;

w is 1, 2, or 3;

x is 0, 1 or 2;

and further wherein, when Ar is (i), (ii) or (iii), and A is $CONR^{46'}$, NHCO, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

E represents (g):



(g);

R^{71} is an optionally substituted 5 to 7-membered saturated or partially saturated heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur or R^{71} is an optionally substituted 6,6 or 6,5 bicyclic ring containing a nitrogen atom and optionally a further heteroatom selected from oxygen, nitrogen or sulfur;

R^{72} is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{74}R^{75}$, CO_2R^{76}, trifluoromethyl, $NHCO_2R^{77}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_zR^{78}$, $SO_2NR^{79}R^{80}$, or halogen;

R^{73} is hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy or halogen, or R^{73} and $R^{46'}$ taken together from a group -X- where X is $(CR^{81}R^{82})_{aa}$ or X is $(CR^{81}R^{82})_{ab}$-Y and Y is oxygen, sulfur or $CR^{81}=CR^{82}$;

R^{74}, R^{75}, R^{76}, R^{79}, R^{80}, R^{81}, and R^{82} are independently hydrogen or C_{1-6}alkyl;

R^{77} and $R^{78}$are independently C_{1-6}alkyl;

y is 1 or 2;

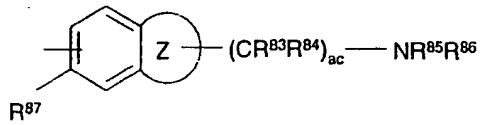
z is 0, 1, or 2;

aa is 2, 3 or 4;

ab is 0, 1, 2 or 3;

and further wherein, when Ar is (i), (ii) or (iii), and A is $CONR^{46'}$, NHCO, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

E represents (a):



(h);

R^{83} and R^{84} are independently hydrogen or C_{1-6}alkyl;

R^{85} and R^{86} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, $CONR^{88}R^{89}$, $NR^{90}R^{91}$, hydroxy, $OCOR^{92}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{93}$, and $NHCO_2R^{94}$;

R^{87} is hydrogen or C_{1-6}alkyl, C_{1-6}alkoxy, or halogen, or R^{87} together with $R^{46'}$ forms a group -AA- where AA is $(CR^{95}R^{96})_{ad}$ or AA is $(CR^{95}=CR^{96})_{ae}$-AB and AB is oxygen, sulfur, $CR^{95}=CR^{96}$, $CR^{95}=N$, $CR^{95}NR^{96}$ or N=N;

Z is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;

R^{88}, R^{89}, R^{90}, R^{91}, R^{92}, R^{95}, and R^{96} are independently hydrogen or C_{1-6}alkyl;

R^{93} and R^{94} are independently C_{1-6}alkyl;

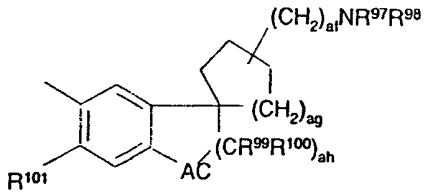
ac is 0 to 4;

ad is 1, 2 or 3;

ae is 0, 1 or 2;

and further wherein, when Ar is (i), (ii) or (iii), and A is $CONR^{46'}$, NHCO, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl,

E represents (i):



(i);

R^{97} and R^{98} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, $CONR^{102}R^{103}$, $NR^{104}R^{105}$, hydroxy, $OCOR^{106}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{107}$, and $NHCO_2R^{108}$;

R^{99} and R^{100} are independently hydrogen or C1-6alkyl;

R^{101} is hydrogen or C_{1-6}alkyl or R^{101} and $R^{46'}$ together form a group -AD- where AD is $(CR^{109}R^{110})$ai or AD is $(CR^{109}R^{110})_{aj}$-AE and AE is oxygen, sulfur or $CR^{109}=CR^{110}$;

AC is oxygen, $CR^{111}R^{112}$ or NR^{113} or AC is a group $S(O)_{ak}$;

R^{102}, R^{103}, R^{104}, R^{105}, R^{106}, R^{109}, R^{110}, R^{111}, R^{112}, and R^{113} are independently hydrogen or C_{1-6}alkyl;

R^{107} and R^{108} are independently C1-6alkyl;

af is 0, 1, 2, 3, or 4;

ag is 1, 2, or 3;

ah is 1, 2, 3 or 4;

ai is 2, 3 or 4;

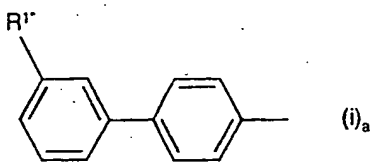
aj is 0, 1, 2, or 3; and

ak is 0, 1 or 2.

Suitably, when Ar is (i) or (ii), the terminal phenyl group in (i) and (ii) can be attached to the phenyl group bearing group A in any position. Preferably the terminal phenyl ring is attached to the phenyl bearing group A in a position meta or para to group A, more preferably para to group A.

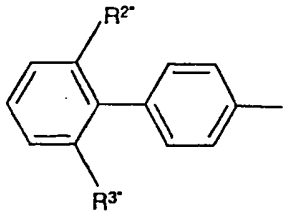
It will be understood that for each moiety $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$ and $R^{6'}$, the ring to which the moiety is attached may contain one or more of the moiety $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$ and $R^{6'}$.

A particularly preferred group of compounds for use herein are those compounds of the formula (I), or a pharmaceutically acceptable salt thereof, wherein, preferably, Ar is represented by sub-formula $(i)_a$:



in which $R^{1"}$ is C_{1-6}alkyl, $COR^{17'}$, $CO_2R^{22'}$, C_{1-6}alkoxy, and $SR^{27'}$, wherein C_{1-6}alkyl is preferably methyl, $R^{17'}$ is preferably C_{1-6}alkyl, $R^{22'}$ is preferably C_{1-6}alkyl, C_{1-6}alkoxy is preferably propoxy, and $R^{27'}$ is preferably C_{1-6}alkyl. More preferably, C_{1-6}alkyl is methyl, $R^{17'}$ is methyl or ethyl, $R^{22'}$ is methyl, ethyl or isopropyl, C_{1-6}alkoxy is propoxy, and $R^{27'}$ is methyl.

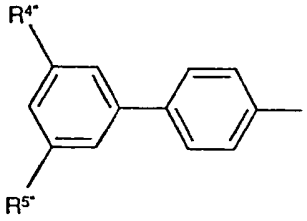
Alternatively, another preferred embodiment of this invention is wherein, preferably, Ar is represented by sub-formula $(i)_b$:



$(i)_b$

in which $R^{2"}$ is C_{1-6}alkyl, trifluoromethyl, C_{1-6}alkoxy, or halogen, and $R^{3"}$ is hydrogen, C_{1-6}alkyl, trifluoromethyl, C_{1-6}alkoxy, or halogen. Preferably, $R^{2"}$ is C_{1-6}alkyl, C_{1-6}alkoxy, or halogen, and $R^{3"}$ is hydrogen, C_{1-6}alkyl, or halogen. More preferably, $R^{2"}$ is methyl, ethyl, methoxy, or chloro, $R^{3"}$ is hydrogen, methyl, or chloro. Most preferably, $R^{2"}$ and $R^{3"}$ are independently methyl or chloro.

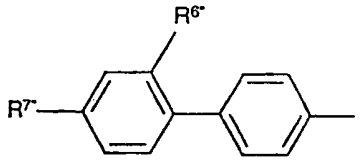
Alternatively, another preferred embodiment of this invention is wherein, preferably, Ar is represented by sub-formula $(i)_c$:



$(i)_c$

in which, $R^{4"}$ and $R^{5"}$ are $CO_2R^{22'}$, wherein $R^{22'}$ is preferably C_{1-6}alkyl, more preferably methyl, or $R^{4"}$ and $R^{5"}$ are halo, preferably chloro.

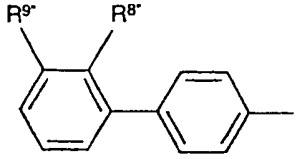
Alternatively, another preferred embodiment of this invention is wherein, preferably, Ar is represented by sub-formula $(i)_d$:



$(i)_d$

in which, $R^{6"}$ and $R^{7"}$ are halo, more preferably chloro.

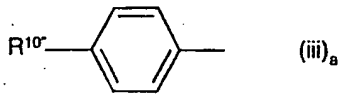
Alternatively, another preferred embodiment of this invention is wherein, preferably, Ar is represented by sub-formula $(i)_e$:



$(i)_e$

in which, $R^{8"}$ and $R^{9"}$ are preferably C_{1-6}alkyl, more preferably methyl.

Alternatively, another preferred embodiment of this invention is wherein, preferably, Ar is represented by sub-formula $(iii)_a$:



$(iii)_a$

in which, $R^{10"}$ is preferably C_{3-6}cycloalkyl, more preferably cyclohexyl, or halo, more preferably iodo.

Suitably, when Ar is $(i)_a$, $(i)_b$, $(i)_c$, $(i)_d$, $(i)_e$, or $(iii)_a$, E represents group (a), (b), (c), (f), (g), (h), or (i). Preferably, when Ar is $(i)_a$, $(i)_b$, $(i)_c$, $(i)_d$, $(i)_e$, or $(iii)_a$, E represents group (a) or (b).

Suitably, when Ar is $(i)_a$, $(i)_b$, $(i)_c$, $(i)_d$, $(i)_e$, or $(iii)_a$, E represents (a). When E represents (a), the groups $-B(CR^1R^2)_a-NR^3R^4$ and R^5 can be attached to the phenyl ring at any position. Preferably the group $-B(CR^1R^2)_a-NR^3R^4$ is located meta or para to group A, more preferably meta to group A and para to group R^6. Preferably the group R^5 is located para to group A. Preferably the group R^5 is alkoxy, more preferably methoxy, or halogen, more preferably iodo. Suitably, A represents $CONR^{46'}$, NHCO, $NHCH_2$, or CH_2NH, where $R^{46'}$ is hydrogen or C_{1-6}alkyl. Preferably group A represents $CONR^{46'}$, where $R^{46'}$ is hydrogen or C_{1-6}alkyl. More preferably A is $CONR^{46'}$ and $R^{46'}$ is hydrogen. Preferably, B is oxygen or CR^7R^8. Preferably, a is 2 or 3. Suitably, R^3 and R^4 are independently C_{1-6}alkyl, preferably isopropyl or tert-butyl; C_{3-7}cycloalkyl, preferably cyclohexyl; or together with the nitrogen atom to which they are attached, form a 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, hydroxy, $OCOR^{12}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{13}$, and $NHCO_2R^{14}$, preferably R^3 and R^4 together with the nitrogen to which they are attached form a 6-membered ring, optionally substituted with one or more of C_{1-6}alkyl, N-acetamido, or hydroxy. R^6 is preferably hydrogen. Preferably, b is 1.

Preferred compounds of formula (I) are wherein, group A represents CONH, E represents (a), and wherein B is oxygen, CR^1R^2 is CH_2 and a is 2, and wherein B is CH_2, CR^1R^2 is CH_2 and a is 2, and wherein B is oxygen, CR^1R^2 is CH_2 and a is

3. Particularly preferred is a compound of formula (I) wherein B is oxygen, CR^1R^2 is CH_2 and a is 2. R^6 is preferably hydrogen.

Suitably, when Ar is $(i)_a$, $(i)_b$, $(i)_c$, $(i)_d$, $(i)_e$, or $(iii)_a$, and E represents (b), the following embodiments are preferred. Suitably, A represents $CONR^{46'}$, NHCO, or CH_2NH, wherein $R^{46'}$ is hydrogen or C_{1-6}alkyl. Preferably group A represents $CONR^{46'}$, where $R^{46'}$ is hydrogen or C_{1-6}alkyl. More preferably A is $CONR^{46'}$ and $R^{46'}$ is hydrogen. The group A can be located at any open position on the phenyl ring. Preferably, the group A is located para to group J. Preferably J is oxygen, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31}, and R^{32}, are preferably hydrogen, h is preferably 1, R^{30} is preferably C_{1-6}alkyl, more preferably C_{3-6}alkyl, most preferably isopropyl, g is preferably 2, and R^{33} is preferably hydrogen.

The term "C_{1-6}alkyl" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

The terms "halo" or "halogen" are used interchangeably herein at all occurrences to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

The terms "cycloalkyl" and "cyclic alkyl" are used herein at all occurrences to mean cyclic radicals, preferably comprising 3 to 7 carbon atoms which may be mono- or bicyclo- fused ring systems which may additionally include unsaturation, including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, 1,2,3,4-tetrahydronaphthyl, and the like.

The term "alkenyl" is used herein at all occurrences to mean a straight or branched chain radical of 2 to 6 carbon atoms, unless the length is limited thereto, wherein there is at least one double bond between two of the carbon atoms in the chain, including, but not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like.

The term "cycloalkenyl" is used herein to mean cyclic radicals, preferably of 5 to 8 carbons, which have at least one double bond between two of the carbon atoms in the ring, including but not limited to cyclopentenyl, cyclohexenyl, and the like.

The term "alkynyl" is used herein at all occurrences to mean a straight or branched chain radical of 2 to 8 carbon atoms, unless the chain length is limited thereto, wherein there is at least one triple bond between two of the carbon atoms in the chain, including, but not limited to, acetylene, 1- propylene, 2-propylene, and the like.

The term "aryl" is used herein at all occurrences to mean 5-14-membered substituted or unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems, including, but not limited to phenyl, naphthyl, and the like.

The term "aralkyl" is used herein at all occurrences to mean an aryl moiety as defined above, which is connected to an alkyl moiety as defined above, for example, benzyl or phenethyl, and the like.

The term "alkoxy" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, bonded to an oxygen atom, including, but not limited to, methoxy, ethoxy, n- propoxy, isopropoxy, and the like.

The terms "hydroxyC_{1-6}alkyl" and "hydroxyalkyl" are used herein interchangeably to mean an hydroxyl group bonded to a C_{1-6}alkyl group as defined above, including, but not limited to methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol, tert-butanol, and the like.

The term "C_{1-4}alkoxyalkyl" is used herein at all occurrences to mean a C_{1-4}alkoxy group as defined above bonded to an alkyl group as defined above, such as an ether, e.g., $-CH_2-CH_2-O-CH_2-CH_2-CH_3$.

The term "hydroxyC_{1-6}alkoxy" is used herein at all occurrences to mean an hydroxyl group bonded to an alkoxy group as defined above, e.g., $-O-CH_2-CH(OH)CH_3$.

The term "C_{1-6}alkoxyC_{1-6}alkoxy" is used herein at all occurences to mean an alkoxy group as defined above, substituted with an alkoxy group as defined above.

The term "acyloxy" is used herein at all occurrences to mean a moiety –O-C(O)-R, wherein R is hydrogen or C_{1-6}alkyl.

The term " C_{1-4}alkanoyl " is used herein at all occurrences to mean a -C(O)C_{1-4}alkyl group wherein the alkyl portion is as defined above.

The term "heterocyclic ring" is used herein at all occurrences to mean a saturated or partially saturated 5-, 6-, or 7-membered ring system (unless the cyclic ring system is otherwise limited) in which the ring system contains one to 3 heteroatoms selected from oxygen, sulfur, or nitrogen, which ring system may be optionally substituted with C_{1-6}alkyl. Examples of such rings include, but are not limited to, piperidine, tetrahydropyridine, and piperazine. When the heterocyclic ring is fused to a phenyl group, the term "heterocyclic ring", together with the phenyl ring to which it is fused, forms a ring which includes, but is not limited to, dihydro-1,4-benzoxazine and 1,2,3,4-tetrahydroquinoline, which may be optionally substituted by C_{1-6}alkyl or oxo.

The term "6,6 or 6,5 bicyclic ring" means a 6,6 or 6,5-bicyclic ring system containing a nitrogen atom and optionally a further heteroatom selected from nitrogen, oxygen, or sulfur, which ring system may be optionally substituted with C_{1-6}alkyl. Examples of such ring systems include, but are not limited to, tropane, isoquinuclidine and granatane rings.

The term "heteroatom" is used herein at all occurrences to mean an oxygen atom, a sulfur atom or a nitrogen atom. It will be recognized that when the heteroatom is nitrogen, it may form an NR_aR_b moiety, wherein R_a and R_b are, independently, hydrogen or C_1 to C_6 alkyl, or together with the nitrogen to which they are bound, form a saturated or unsaturated 5-, 6- or 7-membered ring, including, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, pyridine, and the like. It will be recognized that the saturated or unsaturated 5-, 6- or 7-membered ring may optionally have one or more additional heteroatoms in the ring.

The term "oxo" is used herein at all occurrences to mean a double bonded oxygen atom attached to a chemical moiety as a substituent.

The term "CCR5 mediated disease state" is used herein at all occurrences to mean any disease state which is mediated (or modulated) by CCR5.

Suitably, pharmaceutically acceptable salts of formula (I) include, but are not limited to, salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate, or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate, and stearate.

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like, are equivalent to the unsolvated forms for purposes of this invention.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. The stereocenters may be of any combination of R and S configuration, for example, (R,R), (R,S), (S,S) or (S,R). All of these compounds are within the scope of the present invention.

Among the preferred compounds of the invention are the following compounds:

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2'-ethyl-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2'-methoxy-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',6'-dimethyl-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-ethoxycarbonyl-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',6'-dichloro-1,1'-biphenyl-4-carboxamide.;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2'-chloro-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',4'-dichloro-1,1'-bipheyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-acetyl-1,1'-biphenyl-4-carboxamide trifluoroacetate;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-methylthio-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3',5'-dichloro-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-isopropoxycarbonyl-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3',5'-bis(methoxycarbonyl)-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-propionyl-1,1'-biphenyl-4-carboxamide trifluoroacetate;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-propoxy-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-methoxycarbonyl-1,1'-biphenyl-4-carboxamide trifluoroacetate;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-methyl-1,1'-biphenyl-4-carboxamide trifluoroacetate; and

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',3'-dimethyl-1,1'-biphenyl-4-carboxamide trifluoroacetate.

Among the more preferred compounds of the invention is the following compound:

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-ethoxycarbonyl-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3',5'-dichloro-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-propoxy-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-methyl-1,1'-biphenyl-4-carboxamide trifluoroacetate; and

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',3'-dimethyl-1,1'-biphenyl-4-carboxamide trifluoroacetate.

Formulation of Pharmaceutical Compositions

The pharmaceutically effective compounds of this invention (and the pharmaceutically acceptable salts thereof) are administered in conventional dosage forms prepared by combining a compound of formula (I) ("active ingredient") in an amount sufficient to treat COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection, ("CCR5-mediated disease states") with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1000 mg. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

The active ingredient may also be administered topically to a mammal in need of treatment or prophylaxis of CCR5 mediated disease states. The amount of active ingredient required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the disease state being treated and the mammal undergoing treatment, and is ultimately at the discretion of the

physician. A suitable dose of an active ingredient is 1.5 mg to 500 mg for topical administration, the most preferred dosage being 1 mg to 100 mg, for example 5 to 25 mg administered two or three times daily.

By topical administration is meant non-systemic administration and includes the application of the active ingredient externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous or alcoholic solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally

containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

The active ingredient may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The daily dosage amount of the active ingredient administered by inhalation is from about 0.1 mg to about 100 mg per day, preferably about 1 mg to about 10 mg per day.

In one aspect, this invention relates to a method of treating COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection, all in mammals, preferably humans, which comprises administering to such mammal an effective amount of a CCR5 receptor modulator, in particular, a compound as depicted in formula (I).

By the term "treating" is meant either prophylactic or therapeutic therapy. Such formula (I) compound can be administered to such mammal in a conventional dosage form prepared by combining the formula (I) compound with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other

well-known variables. The formula (I) compound is administered to a mammal in need of treatment for asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection, in an amount sufficient to decrease symptoms associated with these disease states. The route of administration may be oral or parenteral.

The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intra-rectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily parenteral dosage regimen will preferably be from about 30 mg to about 300 mg per day of active ingredient. The daily oral dosage regimen will preferably be from about 100 mg to about 2000 mg per day of active ingredient.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a formula (I) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the formula (I) compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

Methods of Preparation

The compounds of formula (I) can be prepared by art-recognized procedures from known or commercially available starting materials. If the starting materials are unavailable from a commercial source, their synthesis is described herein, or they can be prepared by procedures known in the art.

Specifically, compounds of formula (I) wherein Ar is represented by group (i) or (ii), A is CONH and E is represented by group (a), were prepared according to the methods of international application publication number WO 95/26328, published 5 October 1995 and international application publication number WO 95/15954, published 15 June 1995.

Compounds of formula (I) wherein Ar is represented by group (ii), A is CONH and E is represented by group (f), were prepared according to the methods of international application publication number WO 95/17401, published 29 June 1995.

Compounds of formula (I) wherein Ar is represented by group (i), A is CONH and E is represented by group (g), were prepared according the methods of

international application publication number WO 96/31508 published 10 October 1996.

Compounds of formula (I) wherein Ar is represented by group (i), A is CONH and E is represented by group (c), were prepared according the methods of international application publication number WO 95/30675, published 16 November 1995.

Compounds of formula (I) wherein Ar is represented by group (i), A is CONH and E is represented by group (b), were prepared according the methods of international application publication number WO 96/11934, published 25 April 1996.

Compounds of formula (I) wherein Ar is represented by group (i) or (ii) and A is represented by $CONR^{46'}$ and E is represented by group (a), where $R^{46'}$ and R^6 are represented by group D, where D is $(CR^{22}R^{23})_e$, where e is 2, 3 or 4 and R^{22} and R^{23} are independently hydrogen or C_{1-6}alkyl or D is $(CR^{22}R^{23})_f$-G where f is 0, 1, 2 or 3 and G is oxygen, sulfur or $CR^{22}=CR^{23}$, were prepared according the methods of international application publication number WO 96/06079, published 29 February 1996 and international application publication number WO 95/17398, published 29 June 1995.

Compounds of formula (I) wherein Ar is represented by group (i) or (ii), and A is represented by $CONR^{46'}$ and E is represented by group (h), were prepared according the methods of international application publication number WO 97/07120, published 27 February 1997.

Compounds of formula (I) wherein Ar is represented by group (i) and A is represented by $CONR^{46'}$ and E is represented by group (b), where $R^{46'}$ and R^{33} are represented by the group K, where K is $(CR^{34}R^{35})_j$, where i is 2, 3, or 4 and R^{34} and R^{35} are independently hydrogen or C_{1-6}alkyl or K is $(CR^{34}R^{35})_j$-M where j is 0, 1, 2, or 3 and L is oxygen, sulfur or $CR^{34}=CR^{35}$, were prepared according the methods of international application publication number WO 96/19477, published 27 June 1996.

Compounds of formula (I) wherein Ar is represented by group (i) and A is represented by $CONR^{46'}$ and E is represented by group (i), were prepared according the methods of international application publication number WO 97/19070 published 29 May 1997.

Specifically, compounds of formula (I) wherein Ar is represented by group (i), (ii) or (iii), A is $CONR^{46'}$, NHCO or CH_2NH, and E is represented by group (a), were prepared according to the methods of international application publication number WO 95/15954, published 15 June 1995, international application publication

number WO 95/17398, published 29 June 1995, international application publication number WO 95/26328, published 5 October 1995, international application publication number WO 96/06079, published 29 February 1996, GB 2276161 publishcd 21 September 1994, and GB 2276165 published 21 September 1994.

Compounds of formula (I) wherein Ar is (i) or (ii), and A is $CONR^{46'}$ or NHCO, and E is represented by group (b), were prepared according to the methods of international application publication number WO 96/11934, published 25 April 1996, and WO 96/19477, published 27 June 1996. Other applications cover the spiro compounds WO 97/17350 published 15 May 1997; WO 97/34900 published 25 September 1997; WO 97/34901 published 25 September 1997; WO 97/35861 published 2 October 1997; WO 97/35862 published 2 October 1997.

Compounds of formula (I) wherein Ar is (i), (ii) or (iii), A is $CONR^{46'}$, NHCO or CH_2NH, and E represents (c), were prepared according the methods of international application publication number WO 95/30675 published 16 November 1995 and GB 2276165 published 21 September 1994.

Compounds of formula (I) wherein Ar is (i) or (ii), A is $CONR^{46'}$, and E represents a group (g), were prepared according the methods of international application publication number WO 96/31508, published 10 October 1996.

Compounds of formula (I) when Ar is (i) or (ii), A is $CONR^{46'}$, and E represents group (h), were prepared according the methods of international application publication number WO 95/32967, published 7 December 1995 and WO 97/07120, published 27 February 1997.

Compounds of formula (I) Ar is (i) or (ii), and A is $CONR^{46'}$ or CH_2NH, and E represents group (i), were prepared according the methods of international application publication number WO 97/19070, published 29 May 1997.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. In the Examples, mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment, unless otherwise indicated.

EXAMPLES

Preparation 1

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-4-iodobenzamide

A mixture of 4-iodobenzoyl chloride, prepared from 4-iodobenzoic acid (5.5 g, 22 mmol) and thionyl chloride (20 mL) at 70°C for 30 min followed by removal of thionyl chloride *in vacuo*, 3-(2-diisopropylamino)ethoxy-4-methoxyaniline (WO

95/15954) (5 g, 19 mmol), and diisopropylethylamine (4.9 g, 38 mmol) in dichloromethane (50 mL), was stirred at room temperature for 16 h. The mixture was diluted with dichloromethane, washed with 5% sodium carbonate and with water, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting solid was treated with acetonitrile, filtered, washed with acetonitrile, and dried to give the title compound (8.15 g).

Preparation 2

Preparation of 2',6'-Dichloro-4-biphenylcarboxylic acid

A mixture of 2,6-dichloro-1-iodobenzene (0.5 g, 1.8 mmol), 4-carboxybenzeneboronic acid (0.3 g, 1.8 mmol), tetrakis(triphenylphosphine)-palladium(0) (40 mg), and sodium carbonate (0.68 g, 6.4 mmol) in a 1:1 mixture of 1,2-dimethoxyethane and water (26 mL) was heated at reflux for 16 h. The mixture was cooled and extracted with ether. The aqueous phase was acidified with 3M hydrochloric acid, allowed to stand for 16 h, and filtered. The filter cake was washed with water and dried to give the title compound.

Preparation 3-11

Preparation of 2'-Chloro-4-biphenylcarboxylic Acid; 2',4'-Dichloro-4-biphenylcarboxylic Acid; 3'-Methylthio-4-biphenylcarboxylic Acid; 3',5'-Dichloro-4-biphenylcarboxylic Acid; 3'-Isopropoxycarbonyl-4-biphenylcarboxylic Acid; 3'-Propionyl-4-biphenylcarboxylic Acid; 3'-Propoxy-4-biphenylcarboxylic Acid, 3'-Methyl-4-biphenylcarboxylic Acid, and 2',3'-Diethyl-4-biphenylcarboxylic Acid

Following the procedure of Preparation 2, except substituting 2-chloro-1-iodobenzene, 2,4-dichloro-1-iodobenzene, 3-methylthio-1-bromobenzene, 3,5-dichloro-1-iodobenzene, 3-isopropoxycarbonyl-1-iodobenzene, 3-propionyl-1-bromobenzene, 3-propoxy-1-bromobenzene, 3-methyl-1-bromobenzene, or 2,3-dimethyl-1-bromobenzene for 2,6-dichloro-1-iodobenzene, gave the title compounds:

2'-chloro-4-biphenylcarboxylic acid: mp 282-285°C;
2',4'-dichloro-4-biphenylcarboxylic acid;
3'-methylthio-4-biphenylcarboxylic acid;
3',5'-dichloro-4-biphenylcarboxylic acid;
3'-isopropoxycarbonyl-4-biphenylcarboxylic acid;
3'-propionyl-4-biphenylcarboxylic acid;
3'-propoxy-4-biphenylcarboxylic acid;
3'-methyl-4-biphenylcarboxylic acid; and

2',3'-dimethyl-4-biphenylcarboxylic acid.

Example 1

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-ethoxycarbonyl-1,1'-biphenyl-4-carboxamide

A solution of 3-(ethoxycarbonyl)phenylzinc iodide in tetrahydrofuran (0.5M, 10 mL, 5 mmol) was added to a solution of the compound of Preparation 1 (1 g, 2 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.2 g) in tetrahydrofuran (10 mL) and the mixture was stirred at RT for 16 h. The mixture was treated with saturated aqueous ammonium chloride, extracted with ether, and the combined organic phase was washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (silica gel, 5% methanol/dichloromethane) to give the title compound (0.14 g): MS(ES) m/e 518.8 $[M+H]^+$.

Example 2-4

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2'-ethyl-1,1'-biphenyl-4-carboxamide, N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2'-methoxy-1,1'-biphenyl-4-carboxamide, and N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',6'-dimethyl-1,1'-biphenyl-4-carboxamide

Following the procedure of Example 1, except substituting 2-ethylphenylzinc iodide, 2-methoxyphenylzinc iodide, or 2,6-dimethylphenylzinc iodide for 3-(ethoxycarbonyl)phenylzinc iodide, gave the title compounds:

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2'-ethyl-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 474.9 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2'-methoxy-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 476.9 $[M+H]^+$; and

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',6'-dimethyl-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 474.8 $[M+H]^+$.

Example 5

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',6'-dichloro-1,1'-biphenyl-4-carboxamide

The compound of Preparation 2 (0.25 g, 0.9 mmol), 3-(2-diisopropylamino)ethoxy-4-methoxyaniline (WO 95/15954)(0.26 g, 1 mmol), and benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (0.44 g, 1 mmol) was dissolved in acetonitrile (5 mL), and treated with triethylamine (0.2

g, 2 mmol). The mixture was stirred at RT for 16 h, treated with brine, and extracted with dichloromethane. The organic phase was washed with 5% sodium carbonate and with water, dried ($MgSO_4$), concentrated *in vacuo*, and purified by HPLC (ODS-A, 20 X 50 mm, A:acetonitrile B:water-0.1% trifluoroacetic acid, 10-90% during 10 min, UV detection at 254 nm) to give the title compound: MS(ES) m/e 514.7; 516.8 $[M+H]^+$.

Example 6-15

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2'-chloro-1,1'-biphenyl-4-carboxamide; N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',4'-dichloro-1,1'-biphenyl-4-carboxamide; N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-acetyl-1,1'-biphenyl-4-carboxamide trifluoroacetate; N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-methylthio-1,1'-biphenyl-4-carboxamide; N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3',5'-dichloro-1,1'-biphenyl-4-carboxamide; N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-isopropoxycarbonyl-1,1'-biphenyl-4-carboxamideN-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-propionyl-1,1'-biphenyl-4-carboxamide trifluoroacetate; N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-propoxy-1,1'-biphenyl-4-carboxamide; N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-methyl-1,1'-biphenyl-4-carboxamide trifluoroacetate; and N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',3'-dimethyl-1,1'-biphenyl-4-carboxamide trifluoroacetate

Following the procedure of Example 5, except substituting the compound of Preparations 3 and 4, 3'-acetyl-4-biphenylcarboxylic acid (WO 9743262), or the compounds of Preparations 5-11 for the compound of Preparation 2, afforded the title compounds:

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2'-chloro-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 481.0 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',4'-dichloro-1,1'-bipheyl-4-carboxamide: MS(ES) m/e 515.1 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-acetyl-1,1'-biphenyl-4-carboxamide trifluoroacetate: MS(ES) m/e 489.3 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-methylthio-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 493.3 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3',5'-dichloro-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 515.0 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-isopropoxycarbonyl-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 533.2 $[M+H]^+$;
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-propionyl-1,1'-biphenyl-4-carboxamide trifluoroacetate: MS(ES) m/e 503.1 $[M+H]^+$;
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-propoxy-1,1'-biphenyl-4-carboxamide: MS(ES) m/e 504.4 $[M+H]^+$;
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-methyl-1,1'-biphenyl-4-carboxamide trifluoroacetate: MS(ES) m/e 461.2 $[M+H]^+$; and
N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',3'-dimethyl-1,1'-biphenyl-4-carboxamide trifluoroacetate: MS(ES) m/e 475.2 $[M+H]^+$.

Example 16

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3',5'-bis(methoxycarbonyl)-1,1'-biphenyl-4-carboxamide

A suspension of the compound of Preparation 1 (0.5 g, 1 mmol) in tetrahydrofuran (5 mL) containing dichlorobis(triphenylphosphine)-palladium(II) (34 mg, 0.05 mmol) and 5-(tributylstannyl)-1,3-benzenedicarboxylic acid dimethyl ester [Cielen, et al, *J. Chem. Soc., Perkin Trans.* 2 (1998), 1573-1580] (0.48 g, 1 mmol) was stirred and heated to reflux for 40 h. Additional tetrahydrofuran was added and the mixture heated at reflux for 20 h, cooled, diluted with ether, and filtered through Celite™. The filtrate was diluted with ethyl acetate and decanted to remove insoluble material. The insoluble material was purified by HPLC (ODS-A, 20 X 50 mm, A:acetonitrile B:water-0.1% trifluoroacetic acid, 10-90% during 10 min, UV detection at 254 nm) to give the title compound: MS(ES) m/e 563.1 $[M+H]^+$.

Example 17

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-methoxycarbonyl-1,1'-biphenyl-4-carboxamide trifluoroacetate

A solution of the compound of Example 1 (0.13 g, 0.25 mmol) and sodium methoxide (0.01 g) in methanol (5 mL) was stirred at 65°C for 10 min, cooled, and concentrated *in vacuo*. The residue was dissolved in ethyl acetate, filtered, and the filtrate was dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by HPLC (ODS-A, 20 X 50 mm, A:acetonitrile B:water-0.1% trifluoroacetic acid, 10-90% during 10 min, UV detection at 254 nm) to afford the title compound: MS(ES) m/e 505.0 $[M+H]^+$.

Biological Data:

CCR5 Receptor Binding Assay

CHO cell membranes (0.25 x10^6 cell equivalents) derived from CHO cells stably transfected with CCR5 were incubated with 0.3 ^{125}I-RANTES in a 96 well plate for 45 min. at room temperature (final reaction volume 200 ul). The reaction was terminated by filtration and the filters (GF/C) were washed twelve times with a solution of phosphate buffered saline containing 0.1 % bovine serum albumin and 0.05 % NaN_3. The radioactivity bound to filters was measured by liquid scintillation spectrometry. Non-specific binding was determined in the presence of unlabelled RANTES (10 or 30 nM) and averages 30-50% of total binding.

CCR5 Receptor Functional Assay

The cellular functional assay used to assess antagonist activity of compounds was RANTES-induced Ca^{2+} mobilization in RBL 2H3 cells stably expressing the hCCR5 receptor (RBL 2H3 hCCR5). Agonist activity is determined by Ca^{2+} mobilization in the same cells which is inhibitable by a selective CCR5 antagonist. Cells were grown to 80-100% confluency in T-150 flasks and washed with phosphate-buffered saline. Cells were lifted from the flasks by treating with 3 mL of 1 mM EDTA for 3 min. at room temperature and diluting to 2 X 10^6 cells/mL with Krebs Ringer Henseleit buffer (KRH; 118 mM NaCl, 4.6 mM KCl, 25 mM $NaHCO_3$, 1 mM KH_2PO_4 and 11 mM glucose) containing 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% BSA and centrifuged at 200g for 3 min. Cells were resuspended at 2 X 10^6 cells/mL in the same buffer with 2 μM Fura-2AM, and incubated for 35 min. at 37° C. Cells were centrifuged at 200 x g for 3 min. and resuspended in the same buffer without Fura-2AM, then incubated for 15 min. at 37° C to complete the hydrolysis of intracellular Fura-2AM, and then centrifuged as before. Cells (10^6 cells/mL) were resuspended in cold KRH with 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% gelatin and maintained on ice until assayed. For antagonist studies, aliquots (2 mL) of cells were prewarmed at 37° C for 5 min. in 3 mL plastic cuvettes and fluorescence measured in a fluorometer (Johnson Foundation Biomedical Group, Philadelphia, PA, USA) with magnetic stirring and temperature maintained at 37° C. Excitation was set at 340 nm and emission set at 510 nm. Various concentrations of antagonists or vehicle were added and fluorescence monitored for ~15 sec to ensure that there was no change in baseline fluorescence, followed by the addition of 33 nM RANTES. Maximal Ca^{2+} attained after 33 nM RANTES stimulation was calculated as described by Grynkiewicz *et al.*, (1985). The percent of maximal RANTES-induced Ca^{2+} was determined for each concentration of antagonist and the IC_{50}, defined as the

concentration of test compound that inhibits 50% of the maximal 33 nM RANTES response, obtained from the concentration-response curves (5-7 concentrations of antagonists).

The compounds of this invention show CCR5 receptor modulator activity having IC_{50} values in the range of 0.0001 to 100 μM. The full structure/activity relationship has not yet been established for the compounds of this invention. However, given the disclosure herein, one of ordinary skill in the art can utilize the present assays in order to determine which compounds of formula (I) are modulators of the CCR5 receptor and which bind thereto with an IC_{50} value in the range of 0.0001 to 100 μM.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration it is believed that one skilled in the art can, given the preceding description, utilize the present invention to its fullest extent. Therefore any examples are to be construed as merely illustrative and not a limitation on the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A method of treating a CCR5-mediated disease state in mammals which comprises administering to a mammal in need of such treatment, an effective amount of a compound selected from:

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2'-ethyl-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2'-methoxy-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',6'-dimethyl-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-ethoxycarbonyl-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',6'-dichloro-1,1'-biphenyl-4-carboxamide.;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2'-chloro-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',4'-dichloro-1,1'-bipheyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-acetyl-1,1'-biphenyl-4-carboxamide trifluoroacetate;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-methylthio-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3',5'-dichloro-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-isopropoxycarbonyl-1,1'-biphenyl-4-carboxamide; or

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3',5'-bis(methoxycarbonyl)-1,1'-biphenyl-4-carboxamide;

or a pharmaceutically acceptable salt thereof.

2. The method as claimed in claim 1, wherein the disease is selected from COPD, asthma and atopic disorders, rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV infection.

3. A compound selected from the group consisting of:

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2'-ethyl-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2'-methoxy-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',6'-dimethyl-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-ethoxycarbonyl-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',6'-dichloro-1,1'-biphenyl-4-carboxamide.;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2'-chloro-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2',4'-dichloro-1,1'-bipheyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-acetyl-1,1'-biphenyl-4-carboxamide trifluoroacetate;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-methylthio-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3',5'-dichloro-1,1'-biphenyl-4-carboxamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3'-isopropoxycarbonyl-1,1'-biphenyl-4-carboxamide; and

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3',5'-bis(methoxycarbonyl)-1,1'-biphenyl-4-carboxamide;

or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/30888

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 31/41, 31/36, 31/135
US CL : 514/364, 466, 651
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/364, 466, 651

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99/01127 A1 (SMITHKLINE BEECHAM CORPORATION) 14 January 1999(14.01.99), see entire document.	1-4
Y	US 4,091,097 A (UMEZAWA et al.) 23 May 1978(23.05.78) column 1, lines 49-54, column 13, line 65 to column 14, line 13, see examples 1-18	1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 21 MARCH 2000	Date of mailing of the international search report 11 APR 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DONNA JAGOE JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL ISA Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/30888

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

WEST, STN, ADISALERTS,ADISINSIGHT, AIDSLINE, BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHNO, CANCERLIT, CAPLUS, CBNB, CEN, CIN, CINFSCI, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL, EMBASE, ESBIOBASE, IFIPAT, INVESTEXT, IPA, JICST-EPLUS, KOSMET. search terms: substituted benzanilide, chemokine receptor or ccr5, autoimmune disease or autoimmune disorder,